REMARKS

The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

Status of Claims

Claims 1, 3, 4 and 6-10 are pending in the application. Claims 1, 3, 4 and 6-10 have been rejected.

The Telephone Interview

Initially, Applicants wish to thank the Examiner, Blessing M. Fubara, for granting and attending the telephone interview, with Applicants' Representative, Guy Levi, Reg. No. 55,376 on February 20, 2009. In the interview, the use of supporting declarations was discussed, and the Examiner indicated she would not object to Applicants submitting a declaration from the inventor, Dr. Siegel and Dr. Stanley Davis, the principal investigator at whose laboratory the work cited in Cheng et al., was carried out. The Examiner was notified that the purpose of providing Dr. Davis' declaration is in support of Applicants arguments traversing the Cheng et al. reference.

CLAIM REJECTIONS

35 U.S.C. § 103 Rejections

In the Office Action, the Examiner rejected claims 1 and 3 under 35 U.S.C. § 103(a), as being unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212.

Specifically, the Examiner repeatedly asserts that: Cheng et al., which describes haloperidol-loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere (abstract), achieved a 10% haloperidol, making it obvious for a person skilled in the art at the

time of filing to modify the Cheng et al. reference and achieve a biodegradable polymer or copolymer, wherein said biodegradable polymer or copolymer consists essentially of polylactide or lactide-co-glycolide copolymer; and between about 20 to 40% haloperidol fabricated into an individual, surgically implantable implant as claimed in the subject application.

Applicants respectfully disagree. It would not have been obvious for a person skilled in the art at the time of filing to obtain Applicants' invention of a surgically implantable drug delivery system, comprising: a biodegradable polymer or copolymer, wherein said biodegradable polymer or copolymer consists essentially of polylactide or lactide-co-glycolide copolymer; and between about 20 to 40% haloperidol fabricated into an individual, surgically implantable implant via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation.

1. Cheng et al., does not disclose an implantable matrix of essentially PLA, PLGA or both comprising between 20-40% Haloperidol and it would not have been obvious for Cheng et al., to use 20-40% haloperidol.

Cheng et al., discloses, describes and illustrates in its tables and figures, an injectible drug depot comprising a 50:50 poly(D,L-lactide-co-glycolide) polymer containing a reported maximum of 3.07% (w/w) Haloperidol and a theoretical maximum initial drug loading of 10% (w/w), due to solubility of the API (Haloperidol) in an organic solvent, dichloromethane (DCM), used for fabrication of the microspheres.

The Examiner admitted previously, that the difference between the claims in the subject Application and Cheng et al., is that the claims in the subject Application recite a range of 20-40% of haloperidol being fabricated into the polymer while Cheng uses 10%. However, the Examiner maintains that Cheng et al., discloses a drug content of from 14.6 to 23.9%, which can allegedly be loaded onto the PLG microspheres and therefore, taking the teaching of Cheng et al., one of ordinary skill in the art at the time the invention was made

would have reasonable expectation of success to formulate haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere in which the drug load is 10% or from 14.6 to 23.9%.

Applicants respectfully disagree. In support, Applicants provide a Declaration provided by Dr. Davis; who is the senior author of the Cheng et al. reference and at whose laboratory the work reported in the Cheng reference was carried out. In his Declaration Dr. Davis states that the actual haloperidol concentrations of 20-40% described in the subject Application could not have been obtained by Cheng et al., and that the maximum loading in the Cheng et al. microspheres was about 10%. Applicants' show that the resulting biodegradable implant has two stage, pseudo zero-order release of actual 20-40% haloperidol loading into the blood of a patient over a period of about 5 months (140 days) making it possible for the implants to maintain therapeutically effective constant concentration of haloperidol in the patient's blood and is capable of being removed immediately upon the observation and determination of the need to do so due to undesirable side effects (See e.g. Page 3, Paragraph 0025). (Davis Declaration at 6 and 11)

Therefore, the Examiner's assertion that the a person of ordinary skill in the art at the time the invention was made, would have reasonable expectation of success to formulate haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere in which the drug load is 10% or from 14.6 to 23.9%, is incorrect.

2. The lower concentration drug depots described by Cheng et al. are significantly different than the implants of the subject application, and it would not have been obvious to modify the implants of the subject Application based on the microspheres described by Cheng et al.

Functionally, the differences between the injectible microsphere drug depot of Cheng and the implants of the present Application translates to: longer effective release of Haloperidol into the patient's blood stream (1-2 months in Cheng et al., vs. 5 months in the present application); and inability to remove the depots if necessary upon the presentation of adverse effects by the patients as soon as those adverse effects are diagnosed and at a time less than 1 month.

There is no reasonable expectation of success in modifying the Cheng et al., reference for delivery of 20-40% Haloperidol, as suggested in the present Application. With regard to the Examiner's assertion that Cheng et al., uses 10% and discloses a possible drug content of from 14.6 to 23.9%, Applicants respectfully disagree.

Begining on page 208, right column, last paragraph, and ending on page 209, left column first paragraph, Cheng et al., states:

> "Increasing the theoretical drug content from 4.75 to 9.09% increased the measured drug content in all three sizes of haloperidol-loaded PLG microspheres being 1.53-,1.14- and1.26-fold, respectively (Table 2). Accordingly, the drug loading efficiency of haloperidol-loaded PLG microspheres decreased with increasing theoretical drug content. A loading-stauration effect of haloperidol in the PLG microspheres may be an explanation of this phenomenon. Boisdron-Celle et al. [13] also found that increasing the theoretical content of drug from 27.5 to 60% only resulted in an increase in the actual drug content from 14.6 to 23.9% and consequently the encapsulation efficiency decreased, suggesting that the entrapment of drug within the microspheres was saturated."

Applicants wish to clarify that it is not Applicants' assertion (see e.g. pp. 5 in Sep. 3, 2008 Office Action, item 6) that the 14.6 to 23.9% drug content is that of 5-fluorouracyl, but rather the authors of reference 13 in the Cheng reference (see e.g. pp. 212, See also Davis Declaration at 12). To further demonstrate this, Applicants have appended the Abstract of Reference 13 (J Pharm Pharmacol. 1995 Feb;47(2):108-14) Title: "Preparation and characterization of 5-fluorouracil-loaded microparticles as biodegradable anticancer drug carriers". Thus it is Applicants' assertion, which is also supported by the Davis declaration provided herein at 12, that indeed, the 14.6-23.9% actual drug loading obtained was with 5-fluorouracil and NOT haloperidol.

It would be clear to the skilled artisan, when reading the full paragraph, rather than the line of "actual drug content from 14.6 to 23.9%" alone, and is further supported by the declaration provided herein, that the Authors' intention in citing Boisdron-Celle et al., was to support the conclusion that due to the decrease encapsulation efficiency (hereinafter "EE"; see pp. 209, left column first paragraph), resulting from Haloperidol saturation, ***the maximumn initial theoretical loading of haloperidol in PLG microspheres was around 10%.*** In other words EE=0% for any theoretical drug concentration that would yield anything

beyond an actual 10% drug loading. Therefore, the assertion of the reported actual drug content is not a suggestion that higher drug content is possible, or for that matter, was obtained with haloperidol. (See also the Davis declaration at 12-13)

Moreover, as shown in Figure 5 of Cheng et al., at higher initial loading of Haloperidol, release rate is accelerated, unlike the results described in the present application showing a decrease in release rate with increasing actual initial loading, thereby teaching away from the subject Application. In the subject Application, unexpectedly, at high Haloperidol concentrations, matrix degradation changes and release rates are affected. As stated in the application on page 3, para. 0025 and 0026, higher Haloperidol loading concentration stabilizes the system, slowing the release rate. In the Siegel Declaration (at 9), Dr. Siegel states that unexpectedly, at 40% Haloperidol concentration, matrix degradation changed and release rates were affected stabilizing the system and slowing the release rate. This shows that the polymer matrix used by Cheng et al., is substantially different than the polymer matrix used in the subject Application.

As stated by Dr. Davis in his Declaration (at 8 and 15) it would be unreasonable to expect initial theoretical concentrations of Haloperidol higher than 10% using the system described by Cheng et al., due to saturation and subsequent crystallization of haloperidol in the system reported in Cheng et al. An attempt to incorporate 20-40% haloperidol into the polylactide or lactide-co-glycolide copolymer, as described in the subject Application would not have been successful.

Accordingly it would have been impossible for the Haloperidol/Polymer system disclosed by Cheng et al., to achieve the 20-40% Haloperidol concentrations obtained in the implants of the subject application and therefore it would not have been obvious to modify the implants of the subject Application based on the microspheres described by Cheng et al.

3. The stated encapsulation efficiency in Cheng et al., teaches a person skilled in the art away from trying to incorporate more than 10% initially, *a-fortiory*, 20-40% as actually incorporated in the subject Application

It was known at the time of filing that the entrapped encapsulant drastically affects the encapsulation efficiency and thereby the attainable maximum loading. Encapsulation efficiency (as mentioned and used by Cheng et al., pp. 209), refers to the ratio between the amount of encapsulant (haloperidol in the present Application) in solution before creating the encapsulating matrix and the amount of the encapsulant in the final matrix to be used (*See* e.g. US Patent Application 20080213346A1). Therefore, Applicants respectfully assert and the Siegel and Davis declarations provided support, it would not have been "obvious to try" higher loading concentrations of Haloperidol beyond the disclosed 10% in Cheng et al., and that Cheng et al., clearly teaches away from the present Application.

For example, Okada et al., (Pharm Res. 1994 Aug;11(8):1143-7), disclosed a maximum drug loading of 12% for leuprorelin acetate in microspheres prepared with copoly(DL-lactic/glycolic acid) or poly(DL-lactic acid) (PLA) using an in-water drying method. Beyond the stated maximum theoretical loading of 15%, the authors reported an increase in initial drug release beyond the desired rate; as well increased the glass transition temperature of the microsphere, thereby affecting diffusion rate of solvent to the microspheres and the subsequent effect on drug release. Likewise, Lam et al., (J. Control. Release. 2000 Jul 3;67(2-3):281-92) reported maximum loading of 15-20% for rhIGF-I in polylactic-co-glycolic acid (PLGA) formulations. Sipahigil and Dortunc (Int J Pharm. 2001 Oct 9;228(1-2):119-28) reported a difference of about 12% in the EE of veraparnil and ibuprophen entrapped in carrageenan beads. Similarly, O'Hagen et al., (J. Virol. 2001 October; 75(19): 9037–9043.) report low EE for DNA on PLG microparticles. Many such examples are in the literature from that time.

In view of these Examples it is clear; and is supported by the Davis Declaration provided herein at 11-13 and 15, that Cheng et al. does not teach or suggest that Haloperidol can be loaded at levels of 14.6 to 23.9%, but that due to the decrease in EE resulting from drug saturation of HALOPERIDOL it would be futile to expect loading much beyond the stated initial theoretical 10%. As such, Cheng et al., teaches away from the present Application and a skilled artisan would not expect 20-40% haloperidol loading from reading about 14.6 to 23.9% 5-fluorouracyl loading, especially when the reference to the higher loading of a different drug is brought in support of the lower stated maximum initial theoretical drug loading.

In addition, reading the Cheng reference, a person of ordinary skill would conclude it is impossible to obtain 20-40% Haloperidol in the present system, a conclusion supported by the declaration provided herein. As Cheng stated, Boisdron-Celle et al., increased the initial drug concentration from 27.5% which gave actual drug content of 14.6% (or 53% encapsulation efficiency), to 60% which gave 23.9% actual drug content (or 40% efficiency). Assuming this trend continues, as suggested and taught by Cheng et al., then EE decreases by 0.4% for each percent increase in initial drug loading. Assuming maximum initial drug content of 100% (w/w) drug/PLG, beyond which it would be impossible to form the microspheres, then at 100% initial drug loading EE would be 24% and the maximum drug loading possible would also be 24%. Thus, even assuming that the drug is haloperidol (which it is not!), based on the Cheng et al., citing Boisdron-Celle et al., it would have been impossible to obtain microspheres with drug loading beyond 24%, *a-fortiori*, 40% as disclosed as actual drug loading in the present application.

Moreover, looking at Table 2 (*See* e.g. Cheng et al., pp. 208), the phenomenon of the effect of initial drug loading on encapsulation efficiency is markedly different for Haloperidol in the same matrix (PLG). Taking the highest possible EE stated in Table 2, increasing initial Haloperidol content from 4.75%, yielding 2.17% actual Haloperidol in the microspheres (EE=45%) to 9.09% yielding 2.64% actual Haloperidol in the microspheres (EE=29%), indicates a decrease of 3.7% in EE with a 1% increase in initial drug loading. That means that beyond 16.9%, encapsulation efficiency is 0%. That demonstrates why Cheng et al., states a maximum ***theoretical initial loading of haloperidol in PLG microspheres is around 10%.*** Alternatively, an increase of 4.34% in initial drug concentration (from 4.75 to 9.09%), yielded an increase of 0.47% in actual drug content in the microspheres (from 2.17 to 2.64). That means 0.11% increase in actual drug content for each % increase in initial drug content beyond 4.75%. Again, at 100% initial drug concentration and ignoring the maximum of 16.9% as calculated above (Beyond which the EE is zero), or the 10% maximum theoretical loading asserted by the Author, the maximum that could be obtained is 12.5% actual Haloperidol in the PLG microsphere.

Under these circumstances and as supported by the Davis declaration provided herein at 8, 12, 14, and 15 ***any*** person skilled in the art knowing about the effect of encapsulant type on EE as described hereinabove, in combination with the teachings away of Cheng et al.,

citing Boisdron-Celle et al., concerning the decrease in EE with increasing initial drug concentration, would have absolutely no reasonable expectation of success in trying to encapsulate 20-40% haloperidol in PLG implants (see also Siegel declaration at 9 and Davis declaration at 17).

Claim 1 as previously presented discloses 20-40% ACTUAL loading of Haloperidol, not THEORETICAL maximal initial loading of 10%. In Cheng et al., the actual loading ranging between 0.74 to 3.07 % (See e.g. Table 2, page 208), representing an order of magnitude difference in the actual loading from the present Application.

4. Modifying the Cheng et al., depots according to the subject Application, would have destroyed the depots, making them inoperable for their stated purpose, thus teaching away from the subject Application – making it unobvious in view of Cheng et al.

Any attempt to incorporate the high concentrations of Haloperidol described in the present Application, would have destroyed the PLG depots disclosed in Cheng et al. Incorporating 20-40% haloperidol into the polylactide or lactide-co-glycolide copolymer, as claimed in the subject Application. Specifically, as described on page 208 of the Cheng et al. reference, using dichloromethane (DCM, see page 204, materials) as the solvent and fixing the PLG content at 50 mg/ml, initial drug (haloperidol) loading above 15% (7.5 mg/50 mg PLG, see e.g. page 208 first paragraph), yielded saturation of haloperidol, resulting in needle crystal larger than 20 μm, which are larger than the largest reported particle size (8μm, see e.g. Table II, page 208). Accordingly, based on the teaching of Cheng et al., any person skilled in the art would refrain from incorporating more than 10% haloperidol in the fear that the potential exceeding of saturation and the resulting crystallization of the drug would adversely affect the release of the drug from the polymer matrix. This is because the release rate would now involve the additional time consuming step of solubilizing the crystal before it becomes active and the destruction of the microspheres by the growing Haloperidol crystal.

As stated by Dr. Davis in his Declaration at 9 and 16; the product produced by Cheng et al. was deemed unacceptable due to saturation and subsequent crystallization of haloperidol in the system reported in Cheng et al., making any attempt to incorporate 20-40% haloperidol into the polylactide or lactide-co-glycolide copolymer, unsuccessful. Accordingly, the proposed modification by the Examiner would render the prior art being

modified unsatisfactory for its intended purpose, negating any suggestion or motivation to do so.

Finally, there is no suggestion or motivation, either in the Cheng et al., reference or in the knowledge generally available to one of ordinary skill in the art, to modify the teachings of Cheng et al., for creating a removable drug delivery system. Rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness *In re Kahn*, 441 F.3d 977, 988, (Fed. Cir. 2006). Here, with an asserted 10% maximum theoretical initial loading, there is no rational underpinning to support the legal conclusion of obviousness in encapsulating 20-40% actual Haloperidol content.

If a proposed modification would render the prior art being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Here, the Examiner suggests that an ordinary person of skill in the art would modify an injectible PLGA microsphere of a desirable small particle size (See e.g. Cheng et al., pp. 204), with stated 10% maximum theoretical Haloperidol loading intended for one to two month release, and make an implant that would fit into a 1 cm incision, containing between 20 and 40% Haloperidol to be released over a five month period, clearly making it inoperable for its intended purpose as an injectible depot. Accordingly, Applicants assert that there is no suggestion or motivation in the Cheng et al., reference to modify it as proposed by the Examiner.

As stated in the declaration by Dr. Davis at 18-19, it would not be possible to recover the depots from the patient and a microsphere system, especially in a system with a mean particle size less than 10 micron as described by Cheng el al., which would comprise many tens or hundreds of thousands of particles depending upon the dose and mean particle size. Moreover, as also noted in the declaration by Dr. Davis at 19, the methods of preparing the depots described in Cheng et al. is different than the preparation method for implant, a fact that would have been appreciated by a person skilled in the art, who would therefore not reasonably expect to be successful in modifying the teachings of Cheng et al. according to the subject application.

Therefore, Cheng et al., does not provide the teaching, suggestion or motivation to modify the Haloperidol content and try and encapsulate 20-40% Haloperidol in PLG matrix. Accordingly, Applicants respectfully request that the Examiner remove the rejection of claims 1 and 3 dependent therefrom under 35 U.S.C. § 103(a) as being unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212.

In the Office Action, the Examiner rejected claims 1 and 7-10 under 35 U.S.C. § 103(a) as being unpatentable over Cheng et al, in view of view of Domb et al. ("Degradable Polymers for Site-Specific Drug Delivery," in polymers for Advanced Technologies, Vol. 3, pp. 279-292, 1992. Specifically, the Examiner asserts that Cheng et al., administers the haloperidol by injecting the composition as a depot. But, the Examiner alleges, implantation/implant reads on depot resulting from depot injections, and it is known to use degradable polymers to deliver drugs to target sites of interest ad described by Domb and carries the advantage that implants are used as site specific drug delivery routes.

Applicants respectfully disagree.

Cheng et al., was discussed above. That discussion applies here and the Domb reference fails to cure that deficiency. Therefore the combined Cheng-Domb references do not teach all the claims' elements.

Therefore neither Cheng et al., nor Domb et al., alone or in combination a.) anticipate the use of surgically implanted, removable implants containing 20-40% haloperidol; and b.) contain any suggestion or motivation to combine the references. Therefore, claims 1 and 7 are patentable over Cheng et al., in view of Domb et al. Since claims 8-10 depend directly or indirectly from one of independent claims 1 or 7, they contain all the limitations of these independent claims and are likewise patentable.

Accordingly, Applicants respectfully request that the Examiner remove the rejection of claims 1 and 7-10 under 35 U.S.C. § 103(a) as unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of Domb et al. ("Degradable

Polymers for Site-Specific Drug Delivery," in polymers for Advanced Technologies, Vol. 3, pp. 279-292, 1992.

In the Office Action, the Examiner rejected Claims 4 and 6 as being unpatentable over Cheng et al., in view of Sidman (US 4,450,150, the '150 Patent). According to the Examiner, Cheng prepares the haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere by solvent evaporation.

Cheng admittedly, does not cast the haloperidol dissolved in the solvent in a mold so that Cheng differs from the invention by not molding the haloperidol-polymer solution. However, it is known that implants that deliver drugs to target sites are molded by compressing or injecting the drug formulation as disclosed by Sidman (column 9, lines 8-12; column 10, lines 51-52; column 18, line 29) making the present Application obvious.

Cheng et al., was discussed above. That discussion applies here and the '150 Patent fails to cure that deficiency. Therefore the combined Cheng-Sidman references do not teach all the claims' elements.

As mentioned above, Cheng does not disclose the 20-40% Haloperidol loading, the surgical implantation and the removability of the implant disclosed in the application's independent claim 4 and the '150 Patent fails to cure that deficiency. Therefore the combined Cheng-'150 Patent references do not teach all the claims' elements.

An obviousness rejection requires a teaching or a suggestion by the relied upon prior art of all the elements of a claim (M.P.E.P. §2142). Since Cheng et al., or the '150 Patent, alone or in combination, do not teach or suggest all the elements of independent claim 4, the Examiner fails to establish a *prima facie* showing that Cheng et al., or the '150 Patent, alone or in combination, teach or suggest every feature of claims 4.

Accordingly, Applicants respectfully request that the examiner remove the rejection of claims 1 and 7-10 under 35 U.S.C. § 103(a) as unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of US Patent No. 4,450,150 to Sidman.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

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